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EDITORIAL COMMENTARY

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Defective Immune Response to SARS-CoV-2 Immunization in Down Syndrome Correlates With Increased Susceptibility to Severe Illness With Infection

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With an incidence of about 1 in every 700 live births, Down syndrome (DS) is the most common chromosomal abnormality, and it is estimated that over 200 000 individuals with DS are currently present in the US population. Clinicians have long known that among their many medical problems, persons with DS are at higher risk for severe illness due to infection, and the underlying reasons for this are already proving to be diverse. Interferon responses, particularly type I, during viral infections are key factors in determining the severity of disease [1], and chromosome 21 includes genes for all 3 types of interferon receptors (type I, IFNAR1 and IFNAR2; type II, IFNGR2; and type III, IL10RB). Studies focused on interferon signaling in DS patients have suggested that many have a mild interferonopathy with elevated receptor gene transcription and receptor expression [2]. In contrast to the increased risk incurred by individuals who have deficient interferon responses [3], patients with DS may respond with overly exuberant interferon responses [4].

In addition to the direct effect on cytokine production and receptor signaling conferred by a gene dosage effect in trisomy 21, the size, structure, and function of the thymus, the essential organ for T-cell differentiation and central tolerance, have been shown to be abnormal in persons with DS, which results in quantitative and qualitative defects in T-cell production and function [5]. The resulting immune dysregulation predictably can result in immunodeficiency with increased susceptibility to infection as well as autoimmunity. However, as with other functional aspects in DS, the degree of immune dysregulation/immunodeficiency is quite variable. Whether antibody responses both to natural infection and to immunization are normal in persons with DS has been controversial, with some studies demonstrating decreased responses and others finding no difference from individuals without DS [6]. One study documented subtle abnormalities in T- and B-cell subsets in subjects with DS with no difference in T-dependent (influenza vaccine) antibody responses but somewhat reduced T-independent (pneumococcal polysaccharide vaccine) antibody responses. Unfortunately, comprehensive studies of this type are vanishingly rare [7].

Clinicians need better data regarding the risk for severe disease that their DS patients face during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In this issue of *The Journal of Infectious Diseases*, there are 2 reports that add to the accumulating information that such patients need special attention and support. The first, by Ku et al [8], reports the results of a large, matched cohort study from the prevaccine period in the SARS-CoV-2 pandemic. The authors studied the course of natural infection in individuals with DS and control subjects matched 1:4 by age, sex, race, and ethnicity using the electronic health record of Kaiser Permanente Southern California. The subjects, both with and without DS, were mainly young adults with a mean age of 27 years. The large size of the Kaiser Permanente patient database permitted close matching of the DS individuals and controls with regard to all variables and comorbidities. Over the observation period in these 2 large groups, 142 of 2541 subjects with DS and 695 of 19 164 controls acquired SARS-CoV-2 infection. The results demonstrate that while the risk of infection was about one-third lower in subjects with DS, possibly due to increased caregiver precautions including isolation, the risk of severe disease including death following SARS-CoV-2 infection was 6-fold higher. Despite the complex phenotype of persons with DS, which often includes multiple comorbidities, these results indicate increased susceptibility to severe infection that is not dependent upon these additional health issues.

The principal criticism that could be raised in the study by Ku et al [8], among those discussed by the authors, is that persons with DS frequently have a variety of other health issues such as cardiovascular disease and diabetes, which are independent risk factors for more severe SARS-CoV-2 disease. The authors included and controlled for many baseline comorbidities in their multivariable analyses, which helps to minimize these possible confounding

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(See the Major Articles by Ku et al on pages XX–XX and Streng et al on pages XX–XX.)

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factors. The large size of their study and the comprehensive matching with the control group considerably strengthen their conclusions.

A mild deficiency in the antibody response to SARS-CoV-2 vaccination by persons with DS has been reported in 2 recent studies, both examining the antibody responses using the BNT162b2 mRNA vaccine in 40 adult individuals with DS compared to healthy controls [9, 10]. The study in this issue by Streng et al [11], which was conducted in the Netherlands as part of the Dutch national immunization program, is a larger study that examines the antibody response to mRNA vaccine (BNT162b2 or mRNA-1273) or adenoviral vector-based vaccine (ChAdOx1) in 214 adults with DS with 93 healthy adult controls. Antibody titers were collected up to 2 months prior to the first vaccine dose, at 21–28 days after the first vaccine dose, and 28 days after the second vaccine dose for the mRNA vaccines. Individuals with evidence of prior infection (antispike protein antibody at the first time point or antinucleocapsid antibody at the second or third time points) were excluded from analysis. All subjects produced a positive response to the vaccine as determined using a previously established cutoff, but the subjects with DS produced on average lower postimmunization antibody titers than the control group after 2 doses of the mRNA vaccines (BNT162b2/mRNA-1273) or the ChAdOx1 vaccine. Interestingly, the antibody titers produced by the individuals with DS also declined significantly with the age of the subjects, producing a widening of the difference between the means in older subjects, something not seen in the control group.

As discussed by Streng et al [11], the matching of DS subjects to controls was less than optimal with the control group including a significantly higher proportion of women. However, the strength of the study lies in its relatively large size, which enabled them to assess the response to both the mRNA and adenovirus vector vaccines. In assessing the response to immunization in persons with DS, it would be interesting in future studies, in addition to measuring serologic responses (including measurement of neutralizing antibody), to examine other immunologic parameters, including T-cell numbers and subsets, antigen-specific T-cell responses, and immunoglobulin levels, and how those may correlate with the age of the subjects and durability of the response compared to a well-matched control group. Accelerated immunologic senescence has been documented in patients with DS [12], and it is likely that the reason postimmunization antibody titers differed increasingly from controls with increasing age is dependent on this phenomenon.

Together, these 2 studies present, first, a strong dataset indicating increased vulnerability of individuals with DS to COVID-19 disease and, second, a likely explanation for at least part of that increased susceptibility—deficient humoral response to immunization in a subset of DS patients. As with other aspects of their genetic condition, individual immune responses to immunization among persons with DS appear to vary widely, with some essentially indistinguishable from normal. However, some of these individuals exhibit a deficiency in their adaptive immune responses, which is likely more pronounced during the course of natural infection compared to the relatively potent effects of a synthetic vaccine and also likely much more deficient in older patients. More research is needed to better understand the underlying mechanisms responsible for this deficiency, and, more important from the patient's viewpoint, to devise improved prophylactic and therapeutic measures.

Notes

References

1. Bastard P, Zhang Q, Zhang SY, Jouanguy E, Casanova JL. Type I interferons and SARS-CoV-2: from cells to organisms. Curr Opin Immunol **2022**; 74:172–82.
2. Chung H, Green PHR, Wang TC, Kong XF. Interferon-driven immune dysregulation in down syndrome: a review of the evidence. J Inflamm Res **2021**; 14:5187–200.
3. Aricò E, Bracci L, Castiello L, Urbani F, Casanova JL, Belardelli F. Exploiting natural antiviral immunity for the control of pandemics: lessons from Covid-19. Cytokine Growth Factor Rev **2022**; 63:23–33.
4. Espinosa JM. Down syndrome and COVID-19: a perfect storm? Cell Rep Med **2020**; 1:100019.
5. Verstegen RHJ, Kusters MAA. Inborn errors of adaptive immunity in Down syndrome. J Clin Immunol **2020**; 40: 791–806.
6. Ugazio AG, Maccario R, Notarangelo LD, Burgio GR. Immunology of Down syndrome: a review. Am J Med Genet Suppl **1990**; 7:204–12.
7. Joshi AY, Abraham RS, Snyder MR, Boyce TG. Immune evaluation and vaccine responses in Down syndrome: evidence of immunodeficiency? Vaccine **2011**; 29:5040–6.
8. Ku JH, Levin MJ, Luo Y, et al. Risk of severe COVID-19 disease in individuals with Down syndrome: a matched cohort study from a large, integrated health care system. J Infect Dis **2022**.
9. Sali M, Carfì A, Di Paola A, et al. SARS-CoV-2 vaccine humoral response in adults with Down syndrome [published online ahead of print 21 April 2022]. Clin Microbiol Infect doi: S1198-743X(22)00213-0.
10. Valentini D, Cotugno N, Scoppola V, et al. Safety and long-term immunogenicity of BNT162b2 vaccine in individuals with down syndrome. J Clin Med **2022**; 11:694.
11. Streng BMM, Bont M, Delemarre EM, et al. Decreased antibody response after severe acute respiratory syndrome coronavirus 2 vaccination in patients with Down syndrome. J Infect Dis **2022**. doi:10.1093/infdis/jiac235.
12. Lambert K, Moo KG, Arnett A, et al. Deep immune phenotyping reveals similarities between aging, Down syndrome, and autoimmunity. Sci Transl Med **2022**; 14:eabi4888.